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(54) Title: NEW USE OF PROSTAGLANDINS			
(57) Abstract			
<p>A method for producing a composition containing prostaglandins, derivatives or analogues thereof for increasing pigmentation of tissues or modified tissues, e.g. hair, is disclosed. Among these, derivatives and analogues of prostaglandin F<sub>2α</sub> and prostaglandin E<sub>2</sub> in particular, have been found suitable for the purpose.</p>			

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### New use of Prostaglandins

The present invention is related to the use of prostaglandins and active derivatives or analogues thereof for increasing pigmentation of tissue, for instance eye, skin and hair of animals, including man. The invention also relates to pharmaceutical or cosmetic compositions for said use, as well as the preparation thereof.

The colour of the eye, skin and hair is determined by the amount of melanin in the cells of these structures. Thus, for instance in the eye the colour is determined by the amount of melanin in the melanocytes of the iris. In persons with brown eyes the melanocytes of the iris contain large amounts of melanin whereas in persons with blue eyes the melanocytes of the iris contain only little melanin. When the light in blue eyes is reflected from the pigment epithelium on the back side of the iris the short wave length blue light is not absorbed making the eye colour appear as blue. In persons with brown irises the light is absorbed by the melanin in the melanocytes making the colour appear as brown. In persons with light brown (hazel) or green-brown irises the melanocytes contain more melanin than in persons with blue eyes but less than in persons with brown eyes.

Individuals with little melanin in the cells of the skin have a light pale colour whereas in individuals with much melanin the colour of the skin appears as brown or black depending on the number of melanocytes and the content of melanin in the cells. Whereas in the eye the iridial melanocytes are regarded as continent, i.e. they do not transfer the melanin granules to adjacent cells, in the skin the melanocytes typically transfer the melanin to keratinocytes and they are therefore regarded as incontinent.

The colour of the hair is determined by the melanocytes

located at the dermal papillas. The melanin from these cells is transferred to the cells of the hair matrix and cortex which subsequently keratinize and form the hair. Thus by stimulating the melanocytes in the vicinity of the hair follicle to produce and donate more melanin to the cells of the hair matrix and cortex it is possible to change the colour of the hair in the direction of dark. The growth of eyelashes is similar to that of the hair with melanocytes in close vicinity to the eyelash follicle. Consequently, stimulating these melanocytes to produce more melanin will make the eyelashes darker.

The regulation of eye, skin and hair colour generally is not well understood. However, certain hormones such as alpha-melanocyte stimulating hormone ( $\alpha$ -MSH), and certain steroid hormones are known to affect pigmentation of the skin. In the normal tanning process of the skin the UV light stimulates directly or indirectly the melanocytes in the skin to produce more melanin which is transferred to the adjacent keratinocytes. There is a continuous proliferation of new keratinocytes and the old ones reach the surface of the skin and by shedding ultimately are removed. Thus, unless the skin is exposed to UV light repeatedly the tanning fades away with time. The factors determining the eye colour or hair colour are not known and UV light e.g. has no or negligible effect on the eye colour.

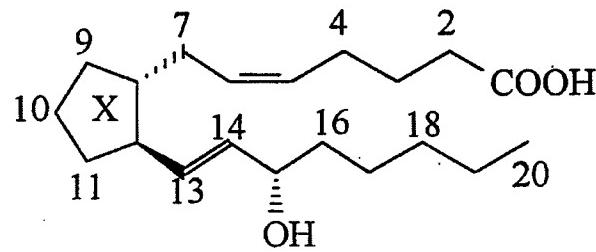
Melanin is a large polymer packed in small granules called melanosomes. There are several kinds of melanin. The most common brown-black melanin is called eumelanin. Another melanin containing cysteine is pheomelanin. Typically the colour of pheomelanin is yellow-red. Individuals with reddish hair have pheomelanin. A third kind of melanin is oximelanin which is black.

We have now unexpectedly found that certain autacoids, more specifically prostaglandins and prostaglandin

derivatives and analogues can be used for increasing pigmentation of body tissues, like skin and iris of the eye, or modified body tissues like hair and eyelashes, when applied topically on the tissue for long periods of time. So can the colour of the eye be altered due to pigmentation of the iris by application of a prostaglandin. Such experiments have been performed in monkeys and the results have recently been verified in man in clinical trials with a prostaglandin analogue. Most unexpectedly, we have also found that in man prostaglandins can alter the colour of the eyelashes. Since the eyelashes are analogous with hair a well-based prediction is that similar treatment of the tissue from which hair is developed will result in a corresponding modification of the colour.

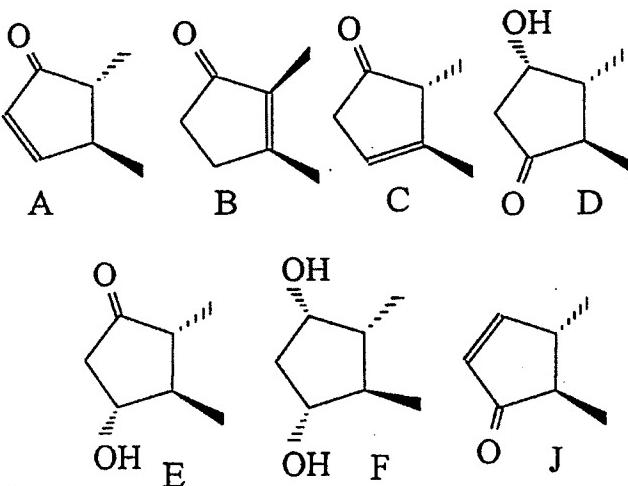
Prostaglandins are a group of components derived from unsaturated 20-carbon fatty acids produced normally by the body. Virtually all tissues of the body produce prostaglandins and other eicosanoids. The prostaglandins have a variety of important physiologic functions and are classified as autacoids, autacoid meaning local hormone. Typically local hormones such as prostaglandins have a consonant effect in the tissue on many different physiological events.

The chemical structure of naturally occurring prostaglandins is illustrated below:



The prostaglandins consist of a cyclopentane ring, denoted "X" in the above formula, and two side chains, the upper one containing 7 carbon atoms being called the alpha chain and the lower one containing 8 carbon atoms being called

the omega chain. The end of the alpha chain is normally a carboxylic acid moiety. The side chains can contain 1 to 3 double bonds, most frequently 2, the double bonds being situated between carbon atoms 5 and 6 on the alpha chain as well as 13 and 14 on the omega chain. The double bond on the alpha chain exhibits cis-configuration, whereas the double bond on the omega chain exhibits trans-configuration. Essential for biological activity is furthermore the substituent group on carbon 15 in the omega chain. In naturally occurring prostaglandins this substituent is hydroxyl. The configuration and functionalities of the cyclopentane ring (X) is important for selectivity to different prostaglandin receptors and the various configurations are depicted below:



Accordingly, prostaglandins are given suffixes A, B, C, D, E, F or J depending on the functionalities of the five membered ring, that is the configuration and substituents of the cyclopentane ring. Noteworthy is that prostaglandins A, B and C probably are not naturally occurring and represent artificial prostaglandins. Nevertheless they exert considerable biologic activity. In order to enhance delivery and to improve chemical stability of prostaglandins the carboxylic acid moiety on the omega chain can be esterified, for instance with alkyl groups containing 1-10 carbons, especially 1-6 carbons.

e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl. Such esterified prodrugs of prostaglandins have been described in several patents and patent applications (see for instance EP 093380, EP 0364417 and WO92/02496). Depending on the specific prostaglandin analogue other derivatives such as salts, e.g. the sodium salt, may also be used.

It is accordingly one objective of the invention to provide a method for increasing the pigmentation of body tissues like the eye and the skin as well as modified body tissues like the hair and the eyelashes by administration of a prostaglandin or an active analogue or derivative thereof, for instance in certain senile and/or pathological conditions. Such conditions comprise e.g.

- depigmentation of the iris causing the iris to become lighter,
- white hair, a condition common among elderly people, and a typical senile change generally perceived negative, and
- vitiligo, a typical disease entity in the skin with hypopigmentation. Vitiligo can occur in many different parts of the body and is perceived as a cosmetic and psychological problem.

According to the mechanism discussed above, which however doesn't limit the invention in any way if found incorrect or incomplete, the invention can alternatively be defined as providing a method for stimulating melanocytes to produce increased amounts of melanin-type substances in animals including man.

Typically the prostaglandins are applied repeatedly for a sustained period of time topically on the part of the body to be treated, for instance the eye, skin or scalp. The active component, the prostaglandin, can be administered by means of aqueous solutions or oil solutions as well as in liniments, creams, ointments, shampoos or in patches, depending on the part of the body to be treated. The

formulations thus have to be adapted to the specific physiological requirements of the organ or tissue to be treated. The solubility and/or stability of the prostaglandin compound may be increased by adding substances forming a complex with the prostaglandin, for instance cyclodextrin-type substances or other compounds known to form complexes, such as inclusion complexes, with hydrophobic compounds.

It is also an objective of the present invention to provide a composition containing an effective amount of at least one prostaglandin or an active analogue or derivative thereof in a physiologically, and pharmacological acceptable carrier for increasing the pigmentation of body tissues like the eye and the skin as well as modified body tissues like the hair and the eyelashes.

For topical use on the eye and the eye lids, the prostaglandins as well as their derivatives and analogues, including esters and salts, can be formulated in aqueous solutions, creams, ointments or oils exhibiting physiologically acceptable osmolarity by addition of pharmacologically acceptable buffers and salts. Such formulations may or may not, depending on the dispenser, contain preservatives such as benzalkonium chloride, chlorhexidine, chlorobutanol, parahydroxybenzoic acids and phenylmercuric salts such as nitrate, chloride, acetate, and borate, or antioxidants, as well as additives like EDTA, sorbitol, boric acid etc. as additives. Furthermore, particularly aqueous solutions may contain viscosity increasing agents such as polysaccharides, e.g. methylcellulose, mucopolysaccharides, e.g. hyaluronic acid and chondroitin sulfate, or polyalcohols, e.g. polyvinylalcohol. Various slow releasing gels and matrices may also be employed as well as soluble and insoluble ocular inserts, for instance based on substances forming in-situ gels. Depending on the actual formulation and

prostaglandin analogue to be used various amounts of the drug and different dose regimens may be employed.

Typically the daily amount of prostaglandin for treatment of the eye might be 0.1-1000 µg/eye, particularly 1-100 µg/eye. To achieve the daily amount of medication depending on the formulation, the prostaglandins may be administered once or several times daily.

For topical use on the skin and the scalp the prostaglandin component can advantageously be formulated using ointments, creams, liniments or patches as carrier.

Also these formulations may or may not contain preservatives depending on the dispenser. Such preservatives comprise as mentioned above e.g. methyl-, propyl- or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and alike. Various matrices for slow release delivery may also be used.

Typically the dose to be applied on the scalp is in the range of 0.0001-100 mg/day, esp. 0.001-100 mg/day, depending on the prostaglandin and the formulation. In a preferred embodiment the dose is 0.001-10 mg/day and especially 0.01-10 mg/day. For the treatment of vitiligo and other skin disorders typically a dose of 0.0001-10 mg/square decimetre/day, like 0.001-1 and esp. 0.01-1 mg/square decimetre/day is employed. To achieve the daily amount of medication depending on the formulation, the prostaglandin may be administered once or several times daily with or without antioxidants.

Several different prostaglandins may be employed to achieve the therapeutic effect on pigmentation in the types of tissues discussed above, e.g. the eye, skin and hair. Particularly prostaglandins of the A, F and E types have been found efficacious. To minimize side effects such as irritation and redness of the eye and skin it may be suitable to use prostaglandin derivatives or analogues which have been found to exert less side effects such as phenyl- and other ring-substituted prostaglandin

derivatives described e.g. in PCT patent publication no: WO90/02553. Prostaglandins exhibiting high pharmacological activity and no or only very small side effects such as 17-phenyl-18,19,20-trinor-PGF<sub>2α</sub> and its carboxylic acid esters may be particularly useful if large areas e.g. of the skin are to be treated. Other prostaglandin analogues exhibiting good therapeutic index may also be used. Generally, since hair growth is slow, the prostaglandins have to be used for sustained periods of time, typically half a year to one year, and if the coloration of the skin or hair is to be preserved the prostaglandin has to be used chronically. It is also possible to use the formulation containing prostaglandins during long term treatment intermittently, e.g. once or twice a week, once every second week or e.g. continuously for a month followed by a month without treatment etc, depending on the potency of the particular prostaglandin.

To achieve increased pigmentation of the iris the prostaglandin formulation has to be administered regularly at least for 3 months or longer. However, in the eye after achieving a certain degree of pigmentation, the prostaglandin can be administered less frequently to maintain the new state of pigmentation e.g. once a week or once a month or possibly even with longer intervals or alternatively with intermittent periods of frequent treatment, e.g. once daily for a month which is followed by a period of 3-12 months of no treatment, followed again by treatment once daily for one month, etc. It may also be possible that the colour change in the iris induced by prostaglandin treatment is permanent and no continuing or intermittent treatment is necessary.

The invention is exemplified with the following non-limiting experiments and clinical data:

Synthesis and formulation of prostaglandin derivatives.PGF<sub>2α</sub> isopropyl ester

This compound was prepared from the commercially available corresponding acid, PGF<sub>2α</sub>. The acid was esterified in acetone with isopropyl iodide in the presence of DBU according to a method described by Grundo R (Organic Prep and Proc Int 1980, 12, 225-228) as a white crystalline product: mp 59-60° C; yield (77%); R<sub>f</sub> = 0.29 (acetone : EtOAc 1:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.89 (t, 3H), 1.2 (d, 6H), 1.3 (m, 6H), 1.5 (m, 3H), 1.68 (m, 2H), 1.8 (m, 2H), 2.05-2.42 (m, 8H), 2.94 (d, 1H), 3.94 (m, 1H), 4.06 (q, 1H), 4.18 (q, 1H), 5 (sept, 1H), 5.34-5.45 (m, 2H), 5.46-5.52 (q, 1H), 5.54-5.60 (q, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.39, 135.19, 132.56, 129.72, 129.00, 78.05, 72.99, 72.89, 67.64, 55.83, 50.46, 42.87, 37.27, 34.06, 31.74, 26.63, 25.68, 25.21, 24.90, 22.61, 21.85, 21.84, 14.02.

PGE<sub>2</sub> isopropyl ester

To a solution of PGE<sub>2</sub> (PGE<sub>2</sub> obtained from Chinoim) (100 mg, 0.28 mmol) in acetonitrile (10 mL), were added ethyl diisopropyl amine (161 mg, 1.3mmol) and isopropyl iodide (380 mg, 2.3 mmol). The reaction mixture was warmed to 60-65° C for 2-3 hours (TLC monitoring). The solution was diluted with diethyl ether (30 mL) and washed with water (20 mL). The water layer was extracted with diethyl ether (30 mL). The combined organic layer was washed with brine (2X10mL), citric acid 5% (2X15 mL), and sodium hydrogen carbonate 5% (3X15 mL). The organic phase was dried on magnesium sulfate, and filtered. The solvent was removed in vacuum to give a colourless oil, which was purified by column chromatography on silica gel using diethyl ether: ethyl acetate (3:1) as eluent, this afforded a colourless oil of PGE<sub>2</sub> isopropyl ester: yield 72mg (64%).

NMR data

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.9(3H, m); 1.22(6H,d); 1.3 (6H, m); 1.4-1.5(2H, m); 1.6-1.7 (2H, m); 2.05 (q, 2H); 2.2-2.4(6H, m);

2.7(1H, m,); 4.05(1H, q); 4.10(1H, q); 5.0(1H, sept)5.30  
(1H, m); 5.43 (1H, m); 5.54(1H, q); 5.64(1H, q).

13,14-dihydro-17-phenyl-18,19,20-trinor PGF<sub>2α</sub> isopropyl ester was prepared according to the method disclosed in PCT publication WO92/02496, which is hereby incorporated by reference.

Effect of prostaglandins on iridial pigmentation in animals.

Cynomolgus monkeys were used. The monkeys were treated topically once daily for 4-12 months with either of the following prostaglandins:

- PGF<sub>2α</sub>-isopropylester 0.5 µg/day, 2 µg/day and 6 µg/day;
- PGE<sub>2</sub>-isopropylester 3 µg/day; and
- 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2α</sub>-isopropyl-ester 2 µg/day, 6 µg/day and 20 µg/day.

The contralateral eye received the vehicle only and served as a control. The frequency of increased iridial pigmentation is shown in Table I. The increase in iridial pigmentation was mostly classified as mild to moderate but in all groups some animals exhibited marked pigmentation. Thus, PGE<sub>2</sub>-isopropylester, PGF<sub>2α</sub>-isopropylester as well as 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2α</sub>-isopropylester all increased iridial pigmentation in an animal model closely reminiscent of the human eye.

Table I. Frequency of increased iridial pigmentation in monkeys after treatment with prostaglandin for 4-12 months.

Prostaglandin	n	Dose (ug/eye)	Duration of treatm. (months)	Animals with pigmentation
PGF <sub>2a</sub> -isopropylester	4	0.5	4	2/4
	4	2.0	4	1/4
	4	6.0	4	3/4
PGE <sub>2</sub> -isopropylester	4	3.0	4	2/4
13,14-dihydro-17-phenyl-18,19,20-trinor-PGF <sub>2a</sub> -isopropylester	10	2.0	12	4/10
	10	6.0	12	6/10
	10	20	12	8/10

After 4-12 months of continuous treatment with prostaglandins the animals were killed and histological sections of the eyes were prepared. Light microscopical pictures clearly demonstrated increased amount of melanin in the melanocytes of the iris.

#### Effect of prostaglandin on iridial pigmentation in man

The results in monkeys have been confirmed in man in clinical trials performed with 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2a</sub>-isopropylester eye drops. After 4.5 to 6 months of continuous treatment with the drug at a dose of approximately 1.5 µg/eye/day (0.005% ophthalmic solution) a change in iridial pigmentation has been observed in patients with green-brown irides. The change in eye colour has been documented with colour photographs taken before treatment and during treatment at regular intervals. The increase in pigmentation has been

classified as mild to moderate. In several of the cases the iris has exhibited depigmented spots or larger areas before treatment, which have been repigmented during treatment with the drug. Thus it is possible that prostaglandin treatment restores normal pigmentation in patients suffering from senile depigmentation. Results obtained in the clinical trials are presented in Table II.

Table II. Occurrence of increased pigmentation of the iris during treatment with 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2a</sub>-isopropylester in patients with elevated intraocular pressure.

Colour of the iris	Duration of treatm. (months)	Dose (ug/eye)	Frequency (%)
Green-brown	4.5-6	1.5	> 20

These results clearly demonstrate that the iridial pigmentation can be increased both in monkeys and in man. A prerequisite for increased pigmentation of the iris in man seems to be a yellow-brown, green-brown or blue/grey-brown colour. There is no other drug known which is able to change the pigmentation of the iris in man.

In addition to the increase in iridial pigmentation in certain patients during treatment with 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2a</sub>-isopropylester eye drops, we have also noticed that some patients get darker eyelashes. The probable explanation for this is that during topical treatment with this prostaglandin analogue part of the drug reaches the follicles of the eyelashes in the eye lids. Thus the melanocytes at the eye lash follicles are stimulated to produce and donate more pigment to the

matrix and cortex cells of the eyelashes and therefore the eyelashes get darker. Since the turnover rate of new eyelashes is approximately 150 days this effect can only be detected during treatment with the drug for long enough periods, approximately 1/2 year.

The implication of the finding with increased pigmentation of the eye-lashes is that hair in general can be made darker with prostaglandins. Thus the hair of the scalp in principle can be treated in the same way with prostaglandins to become darker. Since the hair has a growth rate of approximately 0.5-1 cm/month treatment to convert the colour of the hair will take 6-12 months or longer and to maintain the colour the treatment must continue at regular intervals or intermittently. This indication of prostaglandins may be employed e.g. in individuals suffering from grey or white hair.

Since melanocytes both in the iris and at the eyelash (hair) follicles of the eye lids can be stimulated to produce more melanin by prostaglandins it is evident that melanocytes also in the skin elsewhere can be stimulated by prostaglandins. Thus, a tanning of the skin can be achieved analogously. Such tanning may be desirable from a simple cosmetic point of view but may also be important from a therapeutical point of view in the treatment of certain pathological conditions in the skin such as hypopigmentation e.g. vitiligo.

What claimed is:

1. Use of an active amount of a prostaglandin or an active derivative or analogue thereof for manufacturing a composition for increasing the pigmentation of a tissue or modified tissue, e.g. the iris, skin and hair.
2. Use according to claim 1 in which the prostaglandin is a derivative of PGF<sub>2α</sub>.
3. Use according to claim 1 in which the prostaglandin is a derivative of PGE<sub>2</sub>.
4. Use according to claim 2 in which the prostaglandin is a 17-phenyl-18,19,20-trinor-PGF<sub>2α</sub> derivative.
5. Use according to claim 1 in which the prostaglandin derivative is an ester of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2α</sub>.
6. A method for increasing the pigmentation of tissue or modified tissue, e.g. the iris, skin and hair, comprising administration of an active prostaglandin or a derivative or analogue thereof, as defined in any one of claims 1-5, in a physiologically acceptable formulation to said tissue.
7. Method according to claim 6 in which the prostaglandin is administered to the eye in an amount of 0.1-100 µg/eye daily or at regular intervals.
8. Method according to claim 6 in which the prostaglandin is administered to the scalp in an amount of 0.001-10 mg daily or at regular intervals.
9. Method according to claim 6 in which the prostaglandin is administered to the skin in an amount of approximately 0.0001-10 mg/square decimetre daily or at regular

intervals.

10. A pharmaceutical or cosmetic composition containing an active prostaglandin or a derivative or analogue thereof, as defined in any one of claims 1-5, and a physiologically acceptable carrier, e.g. a solution, ointment, cream, liniment or a patch.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00985

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC6: A61K 7/42, A61K 7/13, A61K 31/557**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC6: A61K**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**SE,DK,FI,NO classes as above**

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE, A1, 4124693 (SCHERING AG BERLIN UND BERGKAMEN), 28 January 1993 (28.01.93)  --	1,6,10
X	EP, A1, 0015658 (AMERICAN CYANAMID COMPANY), 17 Sept 1980 (17.09.80), the abstract; page 3, page 19, example 9  --	1-6,9-10
X	EP, A1, 0302147 (THE PROCTER & GAMBLE COMPANY), 8 February 1989 (08.02.89), the claims; page 1, line 34 - line 43; page 5, line 39 - line 50  --	1-6,9-10
Y	--	8

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	
"E" earlier document but published on or after the international filing date	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"O" document referring to an oral disclosure, use, exhibition or other means	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

30 January 1995

03-02-1995

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00985

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A2, 9404122 (TRUSTEES OF BOSTON UNIVERSITY), 3 March 1994 (03.03.94)	8
A	page 1 - page 2, claims 9-11  --  -----	1-10
A	WO, A1, 8904651 (LVMH RECHERCHE), 1 June 1989 (01.06.89), page 1, line 1 - line 18, abstract  -- -----	1-10

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/SE 94/00985

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 6-9 because they relate to subject matter not required to be searched by this Authority, namely:  
Although Claims 6-9 relate to a method for treating the human or animal body. (see PCT Rule 39.1 (iv)) the search was carried out and was based on the indicated effects of the compounds.
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

31/12/94

International application No.

PCT/SE 94/00985

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